

Claims

5 1. A process for preparing crystalline particles of substance which comprises mixing in a continuous flow cell in the presence of ultrasonic radiation a flowing solution of the substance in a liquid solvent with a flowing liquid anti-solvent for said substance, and collecting the resultant crystalline particles generated, characterised in that the solution and anti-solvent are delivered into the continuous flow cell in parallel contacting streams.

10 2. An apparatus for preparing crystalline particles of a substance which comprises:

(i) a first reservoir of said substance dissolved in a liquid solvent;

(ii) a second reservoir of liquid anti-solvent for said substance;

15 (iii) a mixing chamber having first and second inlet ports and an outlet port;

(iv) means for delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate, which first and second inlet ports are orientated such that the contents of the first and second reservoirs are delivered into the mixing chamber in parallel contacting streams;

20 (v) a source of ultrasonic radiation located in the vicinity of the first inlet;

and

(vi) means for collecting particles suspended in the liquid discharged from the mixing chamber at the outlet port.

25 3. A process according to claim 1 wherein the liquid anti-solvent is miscible with the liquid solvent.

30 4. An apparatus according to claim 2 wherein the liquid anti-solvent is miscible with the liquid solvent.

5. An apparatus according to claims 2 or 4 wherein the first and second inlets protrude into the flow cell such that the liquids outflow into the body of liquid in the mixing chamber.

5 6. An apparatus according to any one of claims 2, 4 and 5 wherein the outflow from the first and second inlets are directed towards the source of ultrasound radiation.

10 7. An apparatus according to any one of claims 2 or 4 to 6 wherein the first and second inlets are adjacent to each other such that the streams of liquid outflowing from each inlet contact along one side of the stream.

15 8. An apparatus according to any one of claims 2 or 4 to 6 wherein the first and second inlets are disposed coaxially such that one inlet completely surrounds the other inlet.

9. An apparatus according to claim 8 wherein the inner inlet is the first inlet (i.e. the inlet for the solution of substance in solvent).

20 10. An apparatus according to claim 2 or 4 to 9 further comprising means to mix the liquids delivered to the mixing chamber via the first and second inlets.

11. An apparatus according to claim 10 wherein the mixing means comprises a stirrer.

25 12. An apparatus according to claim 2 or 4 to 11 wherein the means for delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate comprises one or more pumps.

13. An apparatus according to claim 2 or 4 to 12 wherein the outlet port is disposed above the inlet ports in the mixing chamber such that the liquid in the mixing chamber flows from a lower to a higher point in the chamber before exiting.

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14. An apparatus according to claim 2 or 4 to 13 wherein the mixing chamber is substantially circular in X-section.

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15. An apparatus according to claim 2 or 4 to 14 wherein the means for collecting particles suspended in the liquid discharged from the mixing chamber at the outlet port comprises a filter.

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16. A process according to claim 1 or 3 using an apparatus according to claim 2 or 4 to 15 which comprises:

(i) delivering the contents of the first and second reservoirs to the mixing chamber via the first and second inlet ports respectively at independent controlled flow rate;

(ii) supplying ultrasonic radiation to the vicinity of the inlet ports; and

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(iii) collecting the crystalline particles suspended in the liquid discharged from the mixing chamber at the outlet port.

17. A process according to claim 16 wherein the substance is a pharmaceutical or carrier substance suitable for inhalation therapy.

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18. A process according to claim 17 wherein the substance is fluticasone, beclomethasone, salmeterol, salbutamol or an ester, salt or solvate thereof.

19. A process according to claim 17 wherein the substance is lactose.

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20. A process according to claim 18 wherein the substance is fluticasone propionate.

21. A process according to claim 18 wherein the substance is salmeterol xinafoate.

5 22. A process according to any one of claims 1, 3, 16 or 17 wherein the substance is a mixture.

23. A process according to claim 22 wherein the substance is a mixture of fluticasone propionate and salmeterol xinafoate.

10 24. A process according to claim 20 or claim 23 wherein the solvent is acetone and the anti-solvent is water.

15 25. A process according to claim 21 wherein the solvent is methanol and the anti-solvent is water.

26. A process according to claim 16 wherein the substance is naratriptan hydrochloride.

20 27. A population of particles obtainable by a process according to any one of claims 1, 3 or 16 to 26.

28. A pharmaceutical composition comprising a population of particles according to claim 27.